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GOVERNMENT OF INDIA
THE PATENT OFFICE
NIZAM PALACE, 2ND M.S.O. BUILDING
234/4, ACHARYA JAGADISH BOSE ROAD
KOLKATA – 700 020, INDIA.

TO ALL TO WHOM THESE PRESENTS SHALL COME:

3rd DECEMBER 2003.

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY OF THE PROVISIONAL SPECIFICATION OF THE BELOW IDENTIFIED PATENT APPLICATION NUMBER FILED AT PATENT OFFICE, KOLKATA, INDIA THAT MET THE REQUIREMENTS TO BE GRANTED A DOCUMENT UNDER SECTION 72 OF THE PATENTS ACT, 1970.

PROVISIONAL PATENT APPLICATION NO: 628/CAL/2002

DATE OF FILING: NOVEMBER 7, 2002

By Authority of the
CONTROLLER GENERAL OF PATENTS,
DESIGNS & TRADE MARKS.

(DR. P. C. CHAKRABORTI)
Certifying Officer

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)
APPLICATION FOR GRANT OF A PATENT
(SEE SECTIONS 5(2), 7, 54 AND 135 AND RULE 33A)

1. We, TORRENT PHARMACEUTICALS LTD.
OF CENTRAL PLAZA, 1ST FLOOR, ROOM # - 106,
2/6 SARAT BOSE ROAD, CALCUTTA-700 020,
WEST BENGAL, INDIA,
AND ALSO AT "TORRENT HOUSE", NEAR DINESH HALL,
OFF ASHRAM ROAD, AHMEDABAD - 380009, GUJARAT, INDIA
AN INDIAN COMPANY

2. hereby declare -

(a) that we are in possession of an invention titled "PROCESS FOR PREPARATION OF THE POLYMORPHIC FORM"

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a Patent to us.

3. We further declare that the inventor for the said invention is

NAME (a)	ADDRESS (b)	NATIONALITY (c)
NADKARNI SUNIL SADANAND	TORRENT RESEARCH CENTRE TORRENT PHARMACEUTICALS LTD BHAT 382 428, GANDHINAGAR GUJARAT, INDIA	A CITIZEN OF INDIA

4. That we are the assignees of the true and first inventor.

5. That our address for service in India is as follows:- D. P. AHUJA & CO., 53 Syed Amir Ali Avenue, Calcutta 700 019, West Bengal, India. TEL: 2473158, FAX: 2478982.

6. I, the true and first inventor for this invention declare that the applicant herein are my assignee.

NADKARNI SUNIL SADANAND
TORRENT RESEARCH CENTRE
TORRENT PHARMACEUTICALS LTD
BHAT 382 428, GANDHINAGAR
GUJARAT, INDIA

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachments with the application:

(a) Provisional Specification (3 copies)
(b) Drawings (2 sheets) (3 copies)
(c) Statement and Undertaking on Form-3 (2 copies)
(d) Copy of General Power of Authority
(e) Assignment
(f) Rs.5000/- by cheque bearing No.345852 dated 07/11/2002 on ICICI BANK.

We request that a patent may be granted to us for the said invention.

Dated this 7th day of November 2002.

For: TORRENT PHARMACEUTICALS LTD

Signature :

Name: Mr. Praveen Chand Gandhi

Designation: General Manager.

To
The Controller of Patents,
The Patent Office,
Calcutta.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

TITLE

PROCESS FOR PREPARATION OF THE POLYMORPHIC FORM

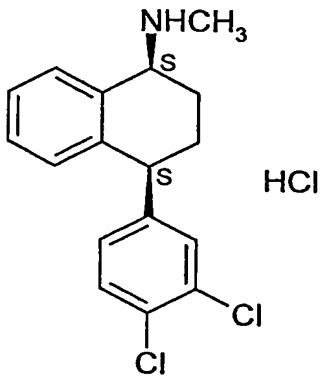
APPLICANT

TORRENT PHARMACEUTICALS LTD.,
OF CENTRAL PLAZA, 1ST FLOOR, ROOM # - 106,
2/6 SARAT BOSE ROAD,
CALCUTTA – 700 020
WEST BENGAL, INDIA
AND ALSO AT "TORRENT HOUSE" NEAR DINESH HALL,
OFF ASHRAM ROAD, AHMEDABAD 380 009,
GUJARAT, INDIA.
AN INDIAN COMPANY.

The following specification describes the nature of the invention.

This invention relates to a process for the preparation of Polymorphic Form V of (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine hydrochloride i.e. Sertraline Hydrochloride. Sertraline Hydrochloride is an agent for treatment for depression, obsessive-compulsive disorder and panic disorder (WO 00/32551).

The need for the drugs, which lack the obstrusive and limiting side effects of the tricyclic antidepressants had prompted the search for agents with greatly enhanced selectivity for specific mechanisms of actions believed to be essential for antidepressant efficacy. Researches targeted for selective competitive inhibitors of synaptosomal serotonin re-uptake, which led to series of 1-methylamine-4-aryltetralins, of which the most promising was the 4-(3,4-dichlorophenyl) analogue. Testing of all possible steroisomers revealed that the required high selectivity for serotonin resides in the cis-1S,4S isomer i.e. (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine hydrochloride (I) commonly known as Sertraline Hydrochloride.



(I)

In the literature various polymorphic Forms of Sertraline Hydrochloride have been described. In light of current interest of pharmaceutical industry, the Polymorphic Form V

is of very much importance (WO 00/32551). Hence, a need was felt to produce the Polymorphic Form V of Sertraline Hydrochloride in bulk by a process which is both efficient and cost-effective.

The "sublimation – condensation method" for preparation of Form V is disclosed in US patent no. 5,248,699. However, the said "sublimation – condensation method" is not practical on a commercial scale, considering the demand of Sertraline Hydrochloride Form - V. This is especially because "sublimation – condensation method" requires special assembly, wherein simultaneously high vacuum and temperature is required to be applied to sublime the starting material, whereas to collect the sublimation product, it invites the special apparatus and skills. Further more, the complexity of the issue is compounded as per the disclosure in WO 0032551, because the "sublimation – condensation method" is not found to be reproducible.

WO 0032551 and WO 0172684 mainly uses Sertraline Hydrochloride (Scheme - 1) or Sertraline base (Scheme - 2) for making Sertraline Hydrochloride Form V.

Scheme – 1

Sertraline Mendalate → Sertraline Base → Sertraline. HCl → Sertraline HCl Form V

Scheme - 2

Sertraline Mendalate → Sertraline Base → Sertraline HCl Form V

Further, WO 0132601 discloses processes for making Sertraline Hydrochloride Form V from using sertraline base. The preparation of Sertraline HCl Form V using the teachings of WO 0132601 Scheme - 3 or Scheme - 4. is as given below:

Scheme - 3

Sertraline Mendalate → Sertraline Base → Sertraline. HCl (Form - CSC 2) → Sertraline HCl Form V.

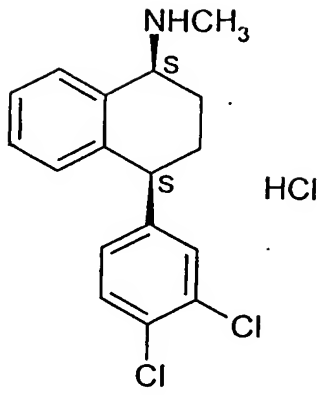
Scheme - 4

Sertraline Mendalate → Sertraline Base → Sertraline. HCl → Sertraline HCl Alcohol Solvate → Sertraline HCl Form V.

As per procedures disclosed in US 5248699, US 4536518, WO 032551, the Sertraline base is prepared using Sertraline mendalate that involves a number of steps implying increase in utilities, manpower, time required to complete the production cycle. Thus, the said processes are commercially expensive.

Thus a need was felt for production of the polymorphic form V of Sertraline Hydrochloride by a simple, efficient and cost effective process.

The objective of the present invention is to provide an efficient and cost effective process for the preparation of the polymorphic Form V of Sertraline Hydrochloride.



(I)

Sertraline Hydrochloride of formula (I) exists in different polymorphic forms, viz. Form I to XVI, T1, CSC - 1, CSC - 2 and amorphous Form. Crystallization for polymorphs is normally done by dissolving or melting the compound followed by gradual or fast cooling of the resultant solution or molten liquid. Different polymorphic forms are identical in solution as evident from their NMR, IR (solution spectra data). On the other hand, solid-state techniques like X-ray or IR (KBr spectra) revealed the difference between polymorphic Forms.

The present invention provides new process for making Sertraline Hydrochloride Form V starting from Sertraline Mandelate.

According to the instant process, Sertraline Mandelate need not be converted into Sertraline base and subsequently into Sertraline Hydrochloride unlike the prior art processes. The multiple steps involved in the prior art processes including an intermediate step for conversion of Sertraline Mandelate into Sertraline Base or Sertraline Hydrochloride or different Form (other than Form V) of Sertraline Hydrochloride is avoided because the present invention provides converting Sertraline Mandelate to Sertraline Hydrochloride Form V directly. Thus, the present invention provides the

manufacturing process, which reduces number of steps implying decrease in utilities, manpower, time required to complete the production cycle. Thus, the instant invention provides a simple one-step process for production of sertraline Hydrochloride Form V in an efficient and cost effective manner.

The polymorphic form V of Sertraline Hydrochloride is prepared according to the instant invention by a process comprising

a) dissolving or suspending Sertraline Mandelate in a solvent

b) reducing the pH of the solution or the suspension, and

c) isolating Sertraline Hydrochloride Form V.

The solvent used for dissolving or suspending Sertraline Mandelate is selected from the group consisting of alcohol, water and mixtures thereof. The alcohols can be selected from methanol, ethanol, n-propanol, isopropanol and mixtures thereof. The preferable solvent is isopropanol.

The dissolving or suspending is achieved by heating and / or stirring. Heating can be done upto 90 °C. Preferably Sertraline mandelate is dissolved at 25-80^{0}C and more preferably at 25 - 30°C under stirring.

The reduction of pH is done by using inorganic acid HCl. HCl is taken in the form of gas or dissolved in a solvent. The solvent can be water or organic solvent or mixtures thereof. The organic solvent can be selected from the solvent such as methanol, ethanol, n-propanol, isopropyl alcohol, tetrahydrofuran, diethyl ether, acetone or mixtures thereof.

Preferably, the reduction of pH is done by using aqueous HCl.

After reduction of pH in the range of 1 - 3, the reaction mixture can be either clear solution or even can be kept in suspention form. The clear solution can be obtained optionally by heating upto 90 °C.

The cooling is effected by allowing the solution to attain room temperature on its own or with mild coolants comprising of cold water, water, alcohols or mixtures thereof. The alcohol is selected from the group comprising of monohydroxy alcohol, dihydroxy alcohol or mixtures thereof. Further, solid obtained can be isolated to get Form V.

The process according to the instant invention is given in Scheme - 5.

Scheme - 5

Sertraline Mendalate → Sertraline HCl Form V

According to a preferred embodiment of the process of the instant invention, Sertraline Mandelate is treated with isopropyl alcoholic HCl. The pH is adjusted to 1-2 and water was added followed by heating the reaction mass to get the clear solution, which after cooling gave directly Sertraline Hydrochloride Form V.

The starting compound Sertraline Mandelate may be prepared according to the procedures disclosed in EP 30081. The preparation of highly pure Sertraline Mandelate is advantageous as it does not demand more time and labour for repeated crystallizations. Sertraline Mandelate is prepared according to the instant invention by a process, wherein purification by repeated crystallization is not required. Also, there is no need to obtain the second crop similar to EP 30081.

A pharmaceutical composition can be obtained by using therapeutically effective amount of Sertraline Hydrochloride Form V thus obtained with a pharmaceutically acceptable carrier.

Brief Description of the Accompanying drawings :

Fig. 1 : This figure indicates X-ray differaction pattern of the compound obtained according to the present invention.

Fig. 2 : This figure indicates IR spectrum of the compound obtained according to the present invention. This is a characteristic infrared absorption spectrum of the polymorphic Form V of Sertraline Hydrochloride of formula (I) in KBr.

The polymorphic Form V of Sertraline Hydrochloride of formula (I) charaterised by the following data:

The Sertraline Hydrochloride that results from practicing the invention as exemplified herein can be characterised by its powder X-ray differaction pattern. Fig. 1 is a representative pattern of Sertraline Hydrochloride Form V. The principal peaks observed are at about 5.2 ± 0.2, 10.4 ± 0.2, 10.9 ± 0.2, 14.1 ± 0.2, 16.3 ± 0.2, 17.1 ± 0.2, 18.4 ± 0.2, 19.0 ± 0.2, 19.7 ± 0.2, 20.9 ± 0.2, 22.0 ± 0.2, 23.0 ± 0.2, 23.5 ± 0.2, 25.3 ± 0.2, 25.9 ± 0.2 and 29.0 ± 0.2 °2 theta.

The IR spectrum of Sertraline Hydrochloride Form V produced by present process is characterized by the following bands:

773 cm^{-1}, 1011 cm^{-1}, 1032 cm^{-1}, 1054 cm^{-1}, 1134 cm^{-1}, 1330 cm^{-1}, 1561 cm^{-1} and 1591 cm^{-1} as shown in figure 2.

FT IR spectrum was recorded in solid state as KBr dispension using Shimadzu FT IR 8700 series FT IR Spectrophotometer.

In the following section preferred embodiments are described by way of examples to illustrate the process of this invention. However, this is not intended in any way to limit the scope of the present invention.

PREPARATORY EXAMPLE

Preparation of Sertraline Mandelate from racemic HCl salt of sertraline.

In a one liter round bottom flask methylene chloride (250 ml), water (250 ml) and racemic HCl salt of Sertraline (50 gm) at room temperature were taken. To it 20% sodium hydroxide solution (10 gm sodium hydroxide solution in 50 ml of water) was added to adjust pH between 9 to 10 as detected on pH paper. Stirred for 45 minutes till clear solution was obtained. Methylene chloride layer was seperated and aqueous layer extracted with methylene chloride twice (50 ml for each extraction). All methylene chloride layers combined and washed with water till the pH reaches at 7 to 8. All methylene chloride layers are collected and distilled out under vacuum at 60°C to get an oil. Methanol 200 ml is charged into it and then heated to 50-55°C. D(-) Mandelic Acid solution (23 gm in 50 ml methanol) added to it at 55-60°C. The temperature raised to 60-65°C and maintained for 10 minutes. The mass cooled to 30-35°C in 1 hr. and further chilled to 20-25°C and temperature maintain at that level for 30 minutes to get solid. The

solid is filtered and washed with acetone 3 times (25 ml each) to get Sertraline Mandelate with dry weight: 28.0 gm.

Preparation of Sertraline Hydrochloride FormV from Sertraline Mandelate

In 1 litre 4 neck round bottom flask equipped with stirrer, theremometer pocket and water condenser, Sertraline Mandelate (25 gm) was added at room temperature. To it, 200 ml of isopropyl alcohol was added under stirring. The pH of the solution was adjusted to 1 to 2 by adding concentrated HCl. To it, 5 ml water was added and heated to reflux to get the clear solution. The solution was filtered through hyflow bed and cooled it to room temperature to get 23 gm of the white solid which was dried further to get 13 gm of dried material of Form V.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to these skilled in the art and are intended to be included within the scope of the present invention.

Dated this 7th day of November, 2002.

(S. D. AHUJA)
of D.P. AHUJA & CO.
APPLICANTS' AGENT

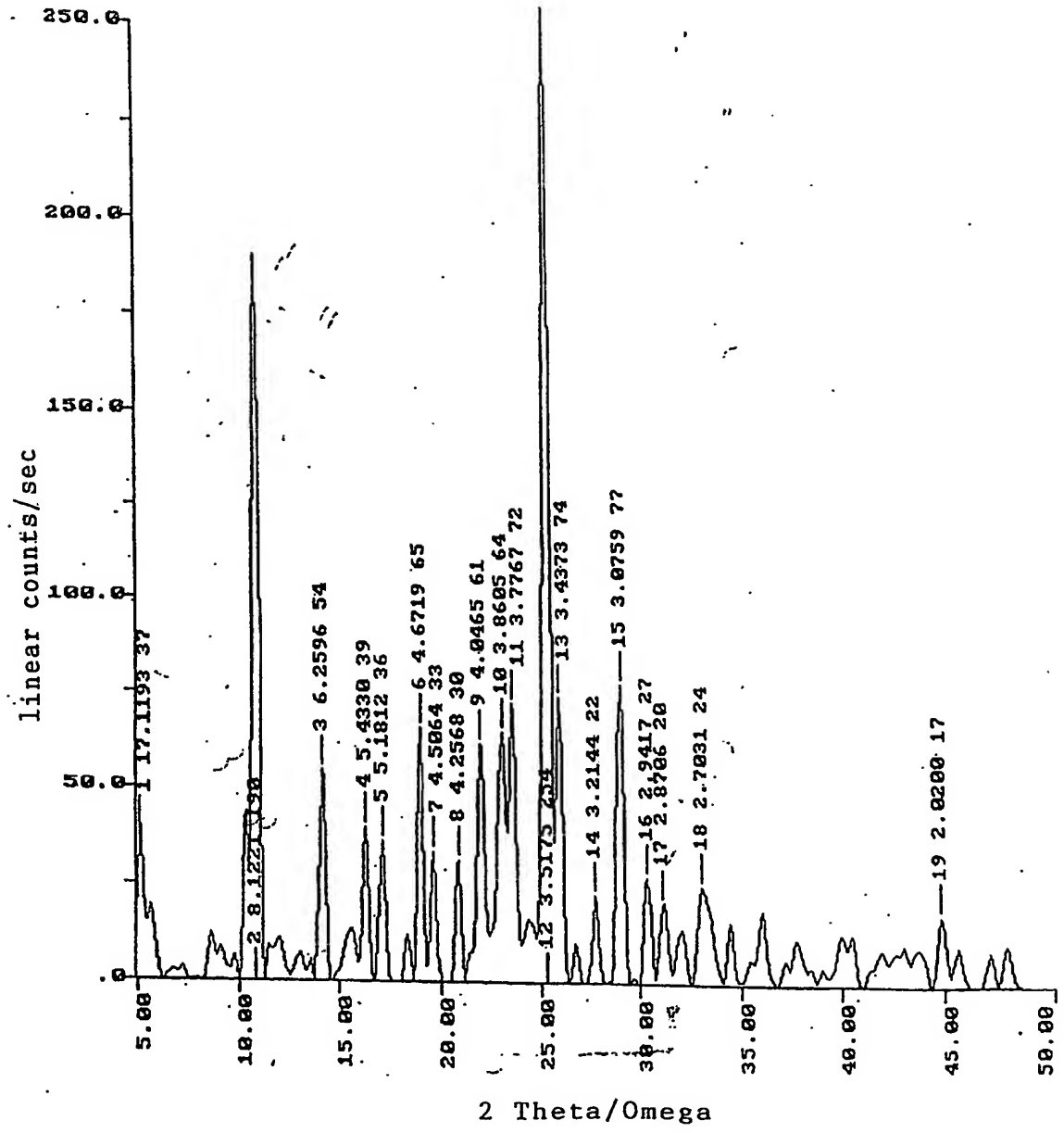
...NT PHARMACEUTICALS LTD.

...PLICATION NO.

PROVISIONAL

2 SHEETS

SHEET 1



(S.R. GUPTA)
of D.P. AHUJA & CO.
APPLICANTS' AGENT

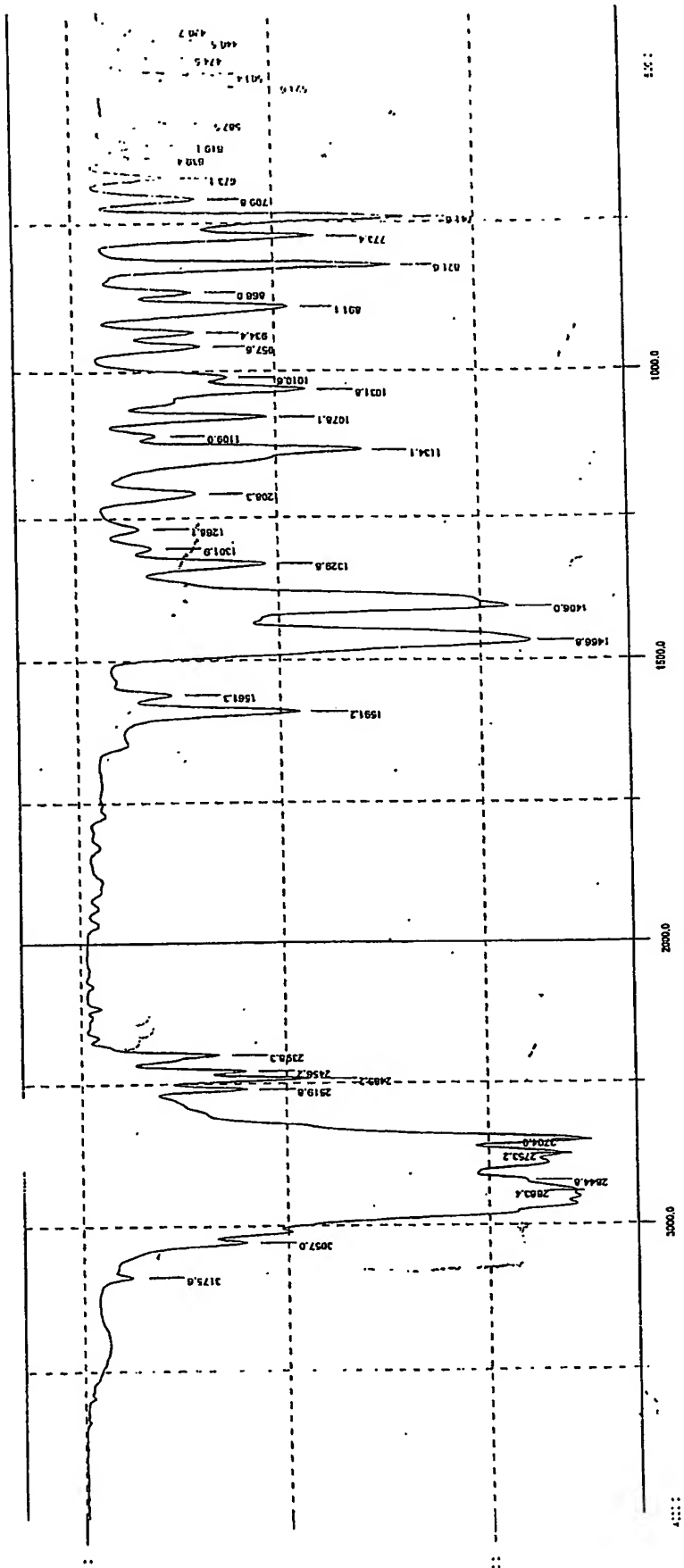
PHARMACEUTICALS LTD.

PROVISIONAL

2 SHEETS

SHEET 2

LICATION NO.



(S.R. GUPTA)
of D.R. AHUJA & CO